REMARKS

Reconsideration of the above-identified application in view of the amendments above and the remarks following is respectfully requested. Claims 14-70 are in this case. Claims 14-70 have been rejected. Claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 34, 36, 38, 40, 42, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64, 66 and 68-70 have now been amended. The specification was also amended on page 54.

Rejections over 35 USC 112, Second paragraph

The Examiner has rejected claims 14-33, 44-67 and 69 over 35 USC 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which Applicant regards as the invention. The rejections of the Examiner are respectfully traversed.

Specifically, the Examiner has rejected claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 40, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64 and 66 as being indefinite because of the recitation of multiple SEQ ID NOs. While continuing to traverse the rejections of the Examiner, in order to expedite the prosecution, Applicant has chosen to amend claims 14, 16, 18, 20, 22, 24, 26, 28, 30, 32, 40, 44, 46, 48, 50, 52, 54, 56, 58, 60, 62, 64 and 66 to recite only SEQ ID NO:10, to conform with the earlier election of SEQ ID NO:10. In addition, Applicant has so amended claims 34, 36, 38 and 42, which also previously recited multiple SEQ ID NOs. Applicant feels that these amendments overcome the rejections of the Examiner in this regard.

The Examiner has also rejected claim 69 with regard to the term "hybridizing", as the Examiner has stated that this term is unclear "absent a statement of the conditions under which the hybridization reaction is performed". While continuing to traverse the rejections of the Examiner, Applicant has added such a statement to claim 69. Support can be found on page 39, lines 1-6.

The Examiner has requested that since PAI1 is an abbreviation, Applicant gives the full name the first time that this term is used in the specification and the claims. To comply with this request of the Examiner, Applicant has amended page 54, lines 14-16, and claim 18 to additionally recite the full name of PAI1, type 1 plasminogen activator inhibitor.

Rejections over 35 USC 112, First paragraph

The Examiner has rejected claims 68-70 under 35 USC 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention. The Examiner has stated that the claims cover all possible preparations comprising a recombinant protein having heparanase catalytic activity, without sufficient limitations.

While continuing to traverse the rejections of the Examiner, Applicant has chosen to amend claims 68-70 to add further limitations. In particular, claims 68 and 70 now have additional limitations related to specific heparanase sequences (support for which can be found as previously described in the last response), while the limitation of specific hybridization conditions has now been added to claim 69 as previously described.

The Examiner has rejected claims 14-63 and 68 over 35 USC 112, first paragraph, as containing subject matter that was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s) had possession of the claimed invention. The rejections of the Examiner are respectfully traversed. As the Examiner has made two sets of rejections under this section with regard to these claims, Applicant has addressed each set of rejections separately.

In a first set of rejections, the Examiner has rejected claims 14, 15, 24, 34, 35, 44, 45, 54, 55 and 68, for including the limitation "wherein said preparation is free of non-heparanase polypeptides encoded by human nucleic acid sequences". The Examiner has rejected claims 16, 17, 26, 27, 36, 37, 46, 47, 56 and 57 for including the limitation "wherein said isolated protein is substantially devoid of glycosylation". The Examiner has rejected claims 18, 19, 28, 29, 38, 39, 48, 49, 58 and 59 for including the limitation "wherein the preparation is substantially free of CXC chemokine or PAI1". The Examiner has rejected claims 20, 21, 30, 31, 40, 41, 50, 51, 60 and 61 for including the limitation "wherein said isolated protein is characterized by insect cell derived sugar prosthetic groups". The Examiner has rejected claims 22, 23, 32, 33, 52, 53, 62 and 63 for including the limitation "wherein said isolated protein is characterized by non-human cell derived sugar prosthetic groups". Applicant respectfully traverses the rejections of the Examiner.

First, with regard to the term "prosthetic group", Applicant notes that in the previous response, Applicant amended the claims to recite "post-translational modifying group". Therefore, the wording rejected by the Examiner was already changed in the previous response.

Applicant further respectfully traverses the rejections of the Examiner as follows. All of these limitations have clear support in the specification, for example with regard to the expression of recombinant heparanase protein in insect cells (see page 78 of the specification). In an insect cell expression system, any resultant preparation will automatically be "free of non-heparanase polypeptides encoded by human nucleic acid sequences", because the only human gene introduced to such a system would be the heparanase gene. Furthermore, Applicant notes that "Molecular Cloning - A Laboratory Manual" (1989) was incorporated by reference on p. 71, lines 19-end of the present application. Therefore, the limitation is supported in the disclosure, and would be clearly recognizable by one of ordinary skill in the art. As noted in the revised Guidelines, a patent specification *preferably omits* that which was known in the art at the time of filing. At the time of filing of the present application, it was clearly known that insect cells will only produce a human protein if a human gene encoding for that protein is introduced to the insect cells; indeed as described in greater detail below, inducing insect cells to produce the human protein from the human gene is non-trivial, and would not automatically be expected to work by one of ordinary skill in the art. However, once the production of the human protein by the insect cells was shown to occur, it would be clear to one of ordinary skill in the art that the preparation would not include any other human proteins, other than that for which the introduced gene encodes.

Similar arguments may be made for the remaining limitations. For example, in microbial or insect cell expression systems, proteins such as CXC chemokines and/or PAI1 are known not to exist, so a heparanase protein produced in one of these expression systems would not be contaminated by one of these proteins. On the other hand, these proteins are well known contaminants of heparanase purified from non-recombinant sources, such as constitutive heparanase expression in mammalian cells.

The Examiner rejected the arguments of Applicant by stating that the above analysis does not justify support for the above limitations. However, Applicant continues

to traverse as the Examiner did not specifically point out why the above references were insufficient to show that one of ordinary skill in the art would easily recognize and appreciate these claimed properties from the specification as it now stands. Furthermore, Applicant feels that these properties were recognized in the disclosure, particularly given the previously described incorporation by reference of "Molecular Cloning - A Laboratory Manual" (1989), which would further enable one of ordinary skill in the art to understand these limitations from the present application.

With regard to the second set of rejections, the Examiner has rejected claims 14-70 as being overly broad, given that the specification describes three amino acid sequences (SEQ ID NOs: 10, 14 or 44) and also nucleic acid sequences encoding for these amino acid sequences, while the claims cover also sequences homologous to these sequences (now narrowed to being homologous to SEQ ID NO: 10). The Examiner has stated that "there is no disclosure of any particular structure to function/activity relationship in the disclosed species".

Applicant amended the above claims and/or added new claims in the previous response (further amended in the current response) in order to narrow the claim recitation to cover polypeptides at least 60% homologous to SEQ ID NO: 10 or a portion thereof". This amendment clearly overcomes the rejections of the Examiner, as a clear structural relationship is drawn between the species disclosed in the specification and the claimed polypeptide. In addition, a clear relationship is drawn between the function of the claimed polypeptide and that of the disclosed species. Applicant therefore feels that these amendments overcome the rejections of the Examiner in this regard.

In particular, Applicant notes that independent claim 70 recites a recombinant protein being characterized by being about 50 or about 65 kDa, and also being characterized according to behavior during a specific purification and assay procedure. This claim therefore recites a simple test which can be used to determine whether a recombinant protein falls within the boundaries of the claim, such that undue experimentation is not required.

Independent claims 68 and 70 now recite a polypeptide or protein being at least 60% homologous to SEQ ID NO: 10 or a portion thereof. Independent claim 69 now recites a specific assay for determining whether a sequence falls within the limitations of

the claims. Independent claims 68-70 now include both structural and sequence limitations.

Applicant specifically traverses the statement of the Examiner that "claims 68-70 have no structural limitations of the claimed polypeptides". As Applicant noted previously, the revised Guidelines state in footnote 42 that "examples of identifying characteristics include sequence, structure, *binding affinity*, binding specificity, *molecular weight* and *length*.... For example, unique cleavage by particular enzymes, isoelectric points of fragments, detailed restriction enzyme maps, *a comparison of enzymatic activities* or antibody cross-reactivity" (emphasis added). Applicant feels that these recited limitations clearly fall within these categories of permissible identifying characteristics, which clearly distinguish the protein of Applicant and which clearly provide structure-function relationships. Therefore, Applicant feels that the claims fully comply with the revised Guidelines in this regard. The Examiner has not stated why this assertion by Applicant is not correct, nor has the Examiner provided any reasoning to explain why the recitation of the claims does not constitute a structural limitation.

Furthermore, Applicant wishes to traverse all of the above rejections of the Examiner with regard to enablement and also written description more generally as follows.

First, the Examiner states on page 11 of the rejection that Applicant's traversal of the rejection of the claims based on lack of enablement is intermixed with the traversal based on lack of written description. However, clearly the two requirements are related. The specification needs to demonstrate that the inventor was in possession of the claimed invention at the time the application was filed. More generally, the written description describes the invention itself, while enablement describes how to make and use the invention. Without a clear description of the invention itself, enablement will not be fulfilled; similarly, without a description of how to make and use the invention, the invention will not be adequately described and hence the written description requirement will not be fulfilled.

Applicant feels, for reasons described in greater detail below, that the present application satisfies both requirements. The written description requirement is clearly fulfilled because the invention (as claimed) is adequately described. The enablement

requirement is clearly fulfilled because a clear description is provided of how to make and use the invention as claimed.

The standard for enablement, as described in *In re Wands*, includes the important concept of undue experimentation. As noted by the Examiner, determination of an amount of experimentation as "undue" may include the following factors: 1) the quantity of experimentation necessary; 2) the amount of direction or guidance presented; 3) the presence or absence of working examples; 4) the nature of the invention; 5) the state of the prior art; 6) the relative skill of those in the art; 7) the predictability or unpredictability of the art; and 8) the breadth of the claims. The Examiner has stated that the above claims which were rejected for lack of enablement were rejected because of undue experimentation. Applicant wishes to specific traverse this rejection and to demonstrate that in fact sufficient enablement relative to the breadth of the claims is provided.

Applicant traverses this rejection, as well as the more general rejection of lack of enablement and also the rejection for lack of written description, on the following general grounds:

1. As chemical entities, DNA/RNA molecules and proteins are entitled to at least similar consideration of enablement as other types of molecules which are routinely claimed with Markush groups.

2. The position of one of ordinary skill in the art, and of those workers in the technological field, is completely at odds with the Examiner's assertion of undue experimentation; indeed, many PhD-level scientists would be rather surprised to learn the Examiner's position concerning how little information about homology is able to provide regarding proteins and nucleic acids, and their expected functions.

3. Furthermore, it is currently not possible to predict with absolute accuracy the function and effect of molecules routinely covered by Markush groups, such as a regular (non-protein or nucleic acid) drug for example, yet broad claim coverage is allowed for entire groups of such molecules on the basis of highly limited examples.

4. The currently structured claims deserve the same consideration as though they were written in the form of Markush groups, because in fact a claim structure

determined on the basis of homology to a nucleic acid or amino acid sequence is functionally equivalent to a Markush group.

As each of these points are discussed at greater length below, Applicant will also address the factors of *Wands* and other issues of enablement and written description, as raised by the Examiner.

NUCLEIC ACIDS AND PROTEINS ARE CHEMICAL ENTITIES

As Applicant noted above, since DNA/RNA molecules and proteins are chemical entities, they are entitled to at least similar consideration of enablement and written description requirements as other types of molecules which are routinely claimed with Markush groups. This concept of nucleic acid molecules and proteins as chemical entities is well established in the case law. For example, *THE REGENTS OF THE UNIVERSITY OF CALIFORNIA V ELI LILLY AND COMPANY* (1997, 43 U.S.P.Q.2D (BNA) 1398) described this concept as part of the decision:

> **A written description of an invention involving a chemical genus, like a description of a chemical species, "requires a precise definition, such as by structure, formula, [or] chemical name," of the claimed subject matter sufficient to distinguish it from other materials.**

Although the above passage relates to written description, it is pertinent to Applicant's arguments regarding both enablement and written description because it demonstrates that the court considered DNA molecules to be chemical species as for previously known molecules.

This concept is reinforced by a further statement in the decision:

> **In claims involving chemical materials, generic formulae usually indicate with specificity what the generic claims encompass. One skilled in the art can distinguish such a formula from others and can identify many of the species that the claims encompass.**

Accordingly, such a formula is normally an adequate description of the claimed genus.

The decision found that the patent in question failed to satisfy these requirements, not because DNA molecules are not chemical entities as understood under US patent law, but rather because the patent failed to meet the regular, known standards for such chemical entities:

In claims to genetic material, however, a generic statement such as "vertebrate insulin cDNA" or "mammalian insulin cDNA," without more, is not an adequate written description of the genus because it does not distinguish the claimed genus from others, except by function. It does not specifically define any of the genes that fall within its definition. It does not define any structural features commonly possessed by members of the genus that distinguish them from others. One skilled in the art therefore cannot, as one can do with a fully described genus, visualize or recognize the identity of the members of the genus.

Again, there is no question raised that would indicate that DNA molecules are different from any other chemical entities. Indeed, the decision specifically raises the issue of how to describe a DNA genus:

A description of a genus of cDNAs may be achieved by means of a recitation of a representative number of cDNAs, defined by nucleotide sequence, falling within the scope of the genus or of a recitation of structural features common to the members of the genus, which features constitute a substantial portion of the genus. This is analogous to enablement of a genus under § 112, P 1, by showing the enablement of a representative number of species within the genus.

The decision then continues by quoting the decision in the court case of *In re Angstadt*, 537 F.2d 498, 190 U.S.P.Q. (BNA) 214 (CCPA 1976) which stated that applicants for a patent "are not required to disclose every species encompassed by their claims even in an unpredictable art". Again, clearly the court looked favorably upon the concept of considering DNA/RNA molecules and proteins as another example of the larger family of chemical entities, deserving of equal consideration as chemical entities.

The Written Description and Enablement requirements of the US Patent and Trademark Office, at least as stated in the rejections by the Examiner, do not appear to take any of the above into consideration. As these requirements are applied by the Examiner, DNA/RNA molecules and proteins become some other type of entities, not molecules at all. Considerations which would not be applied to regular chemistry claims, under the Markush format and Markush practice, somehow become applicable to the present claims.

A particularly noteworthy example (although by no means the only example) of this type of rejection is the statement by the Examiner on page 10 of the office action that "the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable". It should be noted that a similar statement could be made for any type of chemical entity, as the relationship between a chemical formula and the effect and/or the three-dimensional structure(s) of the resulting molecule are also not predictable, nor are they "well understood". If they were predictable and well understood, then drug modeling software could be used to design new drugs in an accurate manner, which is clearly not the case, even when the structure of the target is well known (eg has been crystallized). Thus, the Examiner has imposed a new requirement on proteins which has not been previously imposed on other types of chemical entities. Furthermore, the Examiner has inherently determined that the concept of the Markush group is not applicable as regards DNA/RNA molecules and proteins, since the above statement and the subsequent rejections by the Examiner would actually require testing of *every* species in a genus, as will be demonstrated in further arguments below.

THE POSITION OF THE EXAMINER IS CONTRARY TO STATE OF THE ART

The position and understanding of those scientists in the technological field concerning homology is at odds with the Examiner's assertion of undue experimentation with regard to homology as determined from protein sequences and/or DNA/RNA molecules. These scientists determine the state of the art and the level of the technology, and therefore determine that hypothetical person, PHOSITA or "one of ordinary skill in the art". Indeed, as stated above, many PhD-level scientists would be rather surprised to learn the Examiner's position concerning how little information about homology is able to provide regarding proteins and nucleic acids, and their expected functions.

Indeed, the function of many genes has been identified according to sequence similarity with genes encoding for proteins of known function: see for example **Benner et al.** Res Microbiol. 2000 Mar;151(2):97-106; **Bork & Koonin** Nat Genet. 1998 Apr;18(4):313-8. **Koonin et al.** Proc Natl Acad Sci U S A. 1995 Dec 5;92(25):11921-5. Furthermore, assertions have been made that homologies as low as 30% are sufficient for determining the structure or function of a protein according to that of a known protein (see for example www.ucl.ac.uk/oncology/b11_bioinformatics.ppt, intended as an introduction to bioinformatics and therefore representing the state of the art). Thus, scientists in the field, who presumably play a role in the composite PHOSITA (one of ordinary skill in the art), have confidence in the importance of homology.

The entire Human Genome Project relies upon homology in order to identify the many unknown (at least in humans) genes and the functions of their respective proteins. For example, Human Genome Program, U.S. Department of Energy, *Human Genome News* (v10n1-2) Feb 1999 (www.ornl.gov/TechResources/Human_Genome/publicat/hgn/v10n1/18proteo.html) stated:

> **The availability of entire genomic sequences for some 18 microbes (and many more to come) now offers investigators the opportunity to *perform comparative analysis from an evolutionary perspective, identify conserved genes and metabolic capabilities based on protein sequence homology, and predict protein structures* (emphasis added).**

Homology of proteins and DNA/RNA molecules is an extremely well known tool. Many different databases exist for searching for such sequences according to homology; many different software tools are available for determining such homologies. The value of homology to one of ordinary skill in the art in this field is undoubted, at least to such scientists; however, the Examiner's rejections clearly ignore these very scientists whose work forms the technology and also provides the determination of "ordinary skill in the art", by imposing requirements that no one of ordinary skill in the art would consider as absolute for determining the value of protein or DNA/RNA sequence homologies.

For example, the Examiner (on page 10 of the office action) requires the specification to establish "(A) regions of the protein structure which may be modified without effecting (sic) heparanase catalytic activity; (B) the general tolerance of heparanases to modification and extent of such tolerance; (C) a rational and predictable scheme for modifying any amino acid residue of a heparanase with an expectation of obtaining the desired biological function". A scientist in this field would not consider any of the above requirements to be essential for determining whether a protein is in fact a heparanase or whether it is something else. Instead, the scientist would look to the data based on homology. A degree of homology of 60% or greater would be considered as a very high degree of homology, sufficient to establish a protein as heparanase, particularly in view of the availability of an easily practiced assay (also taught by the present application and described in greater detail below) for confirmation of the activity of the protein as heparanase activity.

The Examiner has also mixed concepts which are separate and distinct according to one of ordinary skill in the art, and which furthermore are not all equally applicable to the technological field of the present invention. The Examiner stated on page 10 of the office action that "the relationship between the sequence of a peptide and its tertiary structure (i.e. its activity) are not well understood and are not predictable". Therefore, the Examiner has clearly conflated the "tertiary structure" of a peptide with "its activity". Yet this combination of the terms is against the understanding of one of ordinary skill in the art. Scientists in this field understand that one can adequately

predict the function of a protein from sequence homology without necessarily knowing the three-dimensional structure of that protein. Therefore, one of ordinary skill in the art would assert that the tertiary structure of a peptide is not essential to determining its function. Thus, such a structure is also not necessary for enabling the present claims.

Applicant does not wish to claim a particular tertiary structure of a peptide. Applicant wishes to claim a peptide having a particular function as defined according to a sequence. Therefore, the tertiary structure of the peptide is not necessary and would certainly not necessarily need to be invoked by one of ordinary skill in the art in order to determine the function of a peptide having a newly discovered sequence. In fact, the opposite is true; given the present state of the art, one of ordinary skill in the art might even place greater reliance on sequence homology, particularly of such a high degree (at least 60%) as for the present claims, given the greater success rate of function following homology than function following tertiary protein structure.

Thus, the rejections of the Examiner are against the state of the technology and the views of scientists in the field, which constitute "one of ordinary skill in the art".

THE EXAMINER'S REJECTIONS ARE CONTRARY TO MARKUSH PRACTICE

It is currently not possible to predict with absolute accuracy the function and effect of molecules routinely covered by Markush groups, such as a regular (non-protein or nucleic acid) drug for example, yet broad claim coverage is allowed for entire groups of such molecules on the basis of highly limited examples.

Ex parte Markush, 1925 C.D. 126; 340 O.G. 839 permits claims for molecules to be constructed in the form of a genus expressed as a group of certain specific items (for example functional groups of a backbone; different molecules for composition claims; etc). Markush group claims are used as there is no other way to provide a chemical invention with a suitable scope of claims.

The importance of the Markush concept was to allow the inventor of a new chemical molecule to actually claim related molecules in a clearly defined manner without being required to separately itemize each individual molecule, and also without being required to demonstrate the function or biological efficacy of each individual molecule. Without this concept, even minor changes in a molecule would fall outside

the scope of chemical claims, because it would not be possible to list every single molecule in a specification.

In terms of enablement, the Markush concept requires demonstration of the function (such as biological activity) of a small number of examples of the group to be sufficient for supporting enablement for the group. Otherwise, as noted above, a Markush group claim would not be possible. Also as previously described, Markush practice provides that the written description requirement can be fulfilled with a Markush group type recitation and the description of a limited number of examples.

As noted in the case law, even in the "unpredictable art" of chemistry, numerous examples of illustrative molecules are not necessarily required (see description above). Furthermore, written description can stand in for examples of illustrative molecules, also as noted in the case law. However, the Examiner's rejections do not address all of these important aspects of the Markush concepts and Markush groups, in order to issue sweeping rejections of the present claims for lack of enablement.

THE PRESENT CLAIMS FOLLOW MARKUSH PRACTICE

The currently structured claims of the present application deserve the same consideration as though they were written in the form of Markush groups, because in fact a claim structure determined on the basis of homology to a nucleic acid or amino acid sequence is functionally equivalent to a Markush group.

As noted above, a Markush group is a way in which to describe a genus by describing the general parameters or characteristics defining the members of the genus or species. Therefore, the Markush group enables a chemical molecule to be claimed, by defining the parameters required to be a member of that group. These parameters usually include a backbone structure with one or more functional groups, each functional group having a defined set of atoms or moieties comprising a plurality of atoms.

The present claims function in the same manner, as they define the genus (heparanase proteins) according to certain characteristics, namely homology of a defined degree relative to a defined sequence. The defined sequence acts as the equivalent of a chemical "backbone"; the percentage homology acts as the functional groups, as it determines any permissible variations on the backbone structure. All of the above

claims relate to a specific stated sequence. All of the above claims relate to homology of a defined percentage, the lowest percentage being 60%. Certain of the claims provide specific guidance on how to determine the percentage of homology in a very specific manner, including the software to be used and parameters for that software, if in fact such specific guidance is even necessary.

As the present claims clearly follow Markush practice, they are deserving of the same consideration as Markush practice for any other molecule or chemical entity, as described above.

These points now lead to consideration of the next issue, the factors determined according to *In re Wands*. According to the rejections of the Examiner, undue experimentation is involved with regard to the present claims, as the specification does not provide sufficient support for the scope of the claims. Applicant wishes to traverse by examining each of the *Wands* factors with regard to the present claims as follows:

Wands factor 1:

Undue experimentation is related to the quantity of experimentation necessary. By "quantity of experimentation" it is clearly meant experimental effort and experimental work. *Wands* itself states that "the test is not merely quantitative, since a considerable amount of experimentation is permissible, if it is merely routine, or if the specification in question provides a reasonable amount of guidance with respect to the direction in which the experimentation should proceed".

The present application actually provides a simple, routine test in order to determine whether a particular protein sequence belongs to the claimed invention. First, selecting a sequence as being homologous (according to a defined percentage of homology) to the sequence stated in the claim is trivial. The present application also provides specific guidance on how to determine homology, including naming a suitable software tool and suitable conditions for operating the tool.

Second, clearly preparing the protein itself from a sequence corresponding to the present claims would be simple, as preparing a vector for a protein of a known sequence, and inserting that vector into a suitable cell line, are both clearly well defined activities for which many commercial kits and tools are available. Applicant notes that the present

application gives further support by noting the suitability of an insect cell line and guidance with regard to the choice of cell line. Thus, the protein could be readily prepared.

Once prepared, the function of the protein could easily be tested as part three, since the present application provides a simple assay for testing heparanase activity. This assay is on the level of a Western blot or any other routine research tool in its simplicity and ease of use.

These three steps are all that is required to test whether a particular protein sequence falls within the present claims:

1. select a sequence according to homology (trivial)
2. produce the protein having that sequence (routine)
3. test the protein for heparanase function (routine)

Thus, the amount of experimentation required is not undue in terms of quantity with regard to the statements in *Wands* itself.

Wands factor 2:

The amount of direction or guidance presented (in the specification). As noted above, the present application provides a great deal of direction and guidance as exactly how to select a protein having heparanase activity and also having the required sequence homology. Since all of the steps of the test are either routine or trivial, no further direction or guidance is required.

Wands factor 3:

The presence or absence of working examples. The present application also provides working examples which are sufficient to demonstrate the claimed invention, particularly given the state of the technological art. After all, there can be no argument that the claimed sequences are protein sequences (or in a few cases protein sequences determined according to nucleotide sequences), nor (since it is specified in the claims) that only those protein sequences producing proteins having heparanase activity are included. The only question raised by the Examiner is whether the resultant proteins have heparanase activity. Since Applicant described a simple test above for determining

such activity, and since the working examples are more than sufficient to describe all of the above aspects of the invention, there are clearly enough working examples.

Wands factor 4:

The nature of the invention. The exact nature of the invention is clear as noted above: proteins having heparanase activity, being determined according to a sequence (with regard to defined homology). Protein sequences have actually become one among many tools for exploring biological function, providing new medicines, and so forth. Proteins themselves are complex chemical entities, but they are still chemical entities, regardless of their complexity (they are actually a type of polymer, which are recognized chemical entities). They should accorded their fair status as a type of chemical entity.

Wands factor 5:

The state of the prior art. This requirement does not seem to be addressed by the rejections of the Examiner. As noted in the present application, routine "cookbooks" for molecular biology existed at the time of filing. Assuming that a protein sequence was known, the gene for the protein could be readily cloned and recombinant protein easily produced. In those cases, such as heparanase, where discovering the sequence was difficult and the initial cloning and production of recombinant protein was also difficult, once the sequence and a suitable method for production were discovered, again recombinant protein could easily be produced: see for example **Shelton DL et al.** J Neurosci. 1995 Jan;15(1 Pt 2):477-91; **Hays WS,** Biochem J. 1996 Nov 1;319 (Pt 3):829-37; **Kitzler JW** Prostaglandins Leukot Essent Fatty Acids. 1996 Oct;55(4):269-77. The test for heparanase activity described in the present application was certainly only a variation on a routine test, given that the art (such as Fuks) cited by the Examiner also includes such a test.

Wands factor 6:

The relative skill of those in the art. Here there can be no doubt; the relative skill of those in this technological art has been recognized in many court decisions as being

quite high, as one of ordinary skill in the art could easily be a team of PhD level scientists. For such individuals, the above tests would be easy and routine to perform.

Wands factor 7:

The predictability or unpredictability of the art. Molecular biology is an unpredictable art, as is chemistry. Applicant does not dispute this fact, but rather questions the apparent assumption in the rejections of the Examiner that molecular biology is somehow *more unpredictable* than chemistry. If anything, molecular biology (or at least the sub-field relating to protein and DNA/RNA sequences) should be *less unpredictable* than the wider field of chemistry. After all, a protein sequence is readily identifiable as such; it will result in a protein and not some other type of chemical. Other non-protein chemical structures are not nearly so clear with regard to the classification of the resultant chemical. Thus, Applicant feels that protein and DNA/RNA sequences should be considered with the same level of unpredictability as regular chemicals, for these reasons and also for the reasons given above.

Wands factor 8:

The breadth of the claims. The breadth of Applicant's claims is actually not overly broad, given that all of the claims are now somehow related to a particular protein sequence. Applicant does not seek to claim every "heparanase", but only those proteins having defined homology to the claimed sequence. Thus, Applicant's claims are actually quite focused.

Thus, in summary, Applicant feels that the following issues have been clearly determined against the rejections of the Examiner:

1. Regarding written description, Applicant has provided a protein sequence, a defined percentage of homology from that sequence, a software tool and parameters for determining homology, and an assay for determining heparanase activity. The present claims also clearly define a genus in terms of the required parameters or characteristics

of species belonging to the genus, as required by Markush practice. Thus, the present application is enabled for written description.

2. Regarding enablement, the above showings clearly also demonstrate that the claimed invention is sufficiently described in the specification so as to allow one of ordinary skill in the art to make or use (practice) the invention without undue experimentation.

3. All of these findings are commensurate with the view of DNA/RNA molecules and proteins as being chemical entities and therefore as being subject to the same requirements as chemical entities.

Rejections over 35 USC 102

The Examiner has rejected claims 64-67, 69 and 70 under 35 USC 102 as being anticipated by US Patent No. 5,362,641 to Fuks et al. et al. (hereinafter "Fuks"). The rejections of the Examiner are respectfully traversed.

Fuks et al. describes the purification of a protein which, as described below, results in the production of a mixture of proteins, of which PAI1 is a significant component, even after all of the described purification procedures of Fuks et al. have been performed. In fact, later evidence has shown that the antibody raised by Fuks et al. against heparanase is actually an anti-PAI1 antibody.

Applicant had previously noted that the antibody of claims 64 and 65 recognizes heparanase, while that of Fuks et al. et al. does not. This antibody characterizes the claimed heparanase. The Examiner is correct in noting that these claims do not cover an antibody, but rather the heparanase protein. However, Applicant respectfully submits that the recitation of an antibody is important for characterization of the protein, and therefore the preparation of Fuks et al. fails in this respect because it failed to elicit an anti-heparanase antibody.

Applicant specifically and respectfully traverses the assertion of the Examiner that the preparation of Fuks et al. et al. is capable of eliciting an anti-heparanase antibody. No proof is provided in this respect, while Applicant has provided ample proof that in fact

this assertion is not correct, for example in the previously submitted affidavit. Furthermore, claims 64 and 65 recite specific sequences, which Fuks et al. neither taught nor suggested and which, as described in greater detail below, required many inventive acts to determine. Therefore, Applicant feels that these arguments overcome the rejections of the Examiner with regard to claims 64 and 65.

Furthermore, claims 66-70 do not recite an antibody as any type of limitation, so regardless of the above rejection by the Examiner with regard to an antibody, Applicant feels that Fuks et al. et al. does not anticipate. In order for a rejection to be made under 35 USC 102, all of the limitations of the claim must be explicitly taught by the reference. Fuks et al. et al. does not teach or suggest particular sequences of any protein, notwithstanding the fact that Fuks et al. failed to purify the heparanase protein. Fuks et al. also does not teach or suggest homologies to a particular protein or amino acid sequence. Fuks et al. does not mention any type of assay for determining whether a particular protein is in fact heparanase, nor does Fuks et al. teach or suggest the presence of glutamic acid residues. Fuks et al. also does not mention any type of hybridization conditions for characterizing a nucleic acid.

In short, Fuks et al. fails to teach or suggest any of the important limitations of claims 66-70. Furthermore, Fuks et al. also fails to render any of these claims obvious, because as previously described in the previously filed Response and Affidavit, actually determining the sequence of heparanase (protein and polynucleotide) *for the first time* proved to be a non-trivial task. Applicant wishes to stress *for the first time* because once the initial sequence was correctly determined, locating other such sequences became a much simpler task. However, short of such an initial sequence determination, the teachings of Fuks et al. would not be sufficient to allow one of ordinary skill in the art to elucidate the sequence of heparanase without undue experimentation. The Examiner has failed to reject any of Applicant's previous arguments in this regard, so Applicant feels that the rejections of claims 66-70 over Fuks et al. should be removed.

Applicant feels that these arguments are further supported by the decision of the court in *In re Duel* (34 USPQ2d at 1215), as follows:

> until the claimed molecules were actually isolated and purified, it would have been highly unlikely for one of ordinary skill in the art to contemplate what was ultimately obtained. What cannot be contemplated or conceived cannot be obvious.

As Applicant noted above, once *one complete sequence* was *correctly identified and isolated*, obtaining further such sequences would be simple. Fuks et al. neither teaches nor suggests a single such sequence. The mere existence of a general method for isolating DNA molecules and determining their sequence was held by the court to be insufficient for a finding of obviousness. Thus, Applicant feels that this overcomes the rejections of the Examiner in this regard.

For the reasons given above, Applicant feels that claims 14-70 are in condition for allowance. A prompt Notice of Allowance is respectfully requested.

Respectfully submitted,

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